SCIENTIFIC LETTER

# Does clopidogrel affect outcome after coronary artery bypass grafting? A meta-analysis

**S Purkayastha, T Athanasiou, V Malinovski, P Tekkis, R Foale, R Casula, B Glenville, A Darzi**

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Antiplatelet agents such as aspirin have been used for many years for the treatment of ischaemic heart disease. More recently, newer drugs such as clopidogrel have been used as single antiplatelet treatment or in conjunction with other antiplatelet drugs to reduce platelet aggregation and therefore lessen the risk of myocardial infarction before and after the insertion of coronary artery stents.[1–3] Clopidogrel is a thienopyridine derivative with a structure and mechanism of action that is distinct from other clinically available antiplatelet agents. Its primary effect appears to be inhibition of ADP induced platelet aggregation without directly affecting arachidonic acid metabolism.[4]

Intermittently patients present for coronary angiography but after imaging it is apparent that operative intervention is required instead of angioplasty despite the continuing use of clopidogrel. These patients may be at increased risk of complications from haemorrhage. In addition, patients with peripheral vascular disease who are being treated with clopidogrel and are potentially at high risk of postoperative adverse events may be referred for cardiac surgery.

Intuitive complications of such potent antiplatelets, such as postoperative haemorrhage, have potentially serious side effects, especially in patients undergoing coronary surgery. Multiple transfusions after cardiac surgery are associated with significant morbidity, mortality, and transmission of viral diseases.[5 6] Several studies have investigated the effect of clopidogrel and postoperative bleeding in patients undergoing cardiac surgery and report varying results.[7 8] No meta-analyses have been done to further substantiate or quantify the findings regarding this subject.

The study aimed at assessing the effect of clopidogrel on postoperative outcome after coronary surgery by comparing patients who were taking clopidogrel at the time of surgery with patients who stopped clopidogrel at least seven days before surgery (control group).

## METHODS

Studies reporting comparative data were retrieved from Medline and the Cochrane database. Quantitative meta-analysis was performed in line with recommendations from the Cochrane Collaboration and the quality of reporting of meta-analyses guidelines,[9] with similar techniques to those that we have used previously.[10] Eleven comparative studies published between 1999 and 2004 of patients undergoing coronary surgery while taking clopidogrel and a control group were used. The study end points were intraoperative blood loss, transfusion requirements, adverse events, ventilation requirements, length of hospital stay, mortality, and re-exploration rates. Random effects model and sensitivity analysis were used and heterogeneity between studies was assessed.

## RESULTS

A combined total of 4002 patients, of whom 605 (15.1%) underwent cardiac surgery while taking clopidogrel and 3397 (84.9%) while not taking clopidogrel, were the basis of the final analysis.

Meta-analysis allowed evaluation of both dichotomous and continuous variables for the measurement of blood loss. This showed a significant increase in blood loss in the clopidogrel group compared with the control group of greater than 300 ml (weighted mean difference (WMD) 323.62, 95% confidence interval (CI) 137.19 to 510.04); however, there was significant heterogeneity between the studies ($\chi^2 = 325.94$, $p < 0.01$). Subgroup analysis of the studies reporting blood loss that presented data on surgery performed without the use of cardiopulmonary bypass also showed a significant increase in blood loss in the clopidogrel group compared with the control group of almost 400 ml (WMD 387.15, 95% CI 3.84 to 770.45), although there was significant heterogeneity between the studies ($\chi^2 = 283.62$, $p < 0.01$). Heterogeneity was reduced, but still significant, after subgroup analysis for studies that were prospective, published from 2003 onwards, and including more than 50 patients in each arm. This showed that study design and sample size were potential causes of heterogeneity.

Overall, the requirement for transfusion of any blood product was significantly increased for the clopidogrel group (odds ratio (OR) 4.90, 95% CI 2.79 to 8.59). This was also shown when the different blood products were considered individually (red cell transfusion: OR 3.64, 95% CI 1.64 to 8.09; platelet transfusion: OR 8.36, 95% CI 3.08 to 22.64; fresh frozen plasma transfusion: OR 3.44, 95% CI 1.40 to 8.43). The overall transfusion requirements for these products were also significant for the clopidogrel group (WMD 1.36, 95% CI 0.80 to 1.92). However, all of these results were associated with significant heterogeneity (table 1).

The incidence of adverse outcomes was significantly higher in the clopidogrel group than in the controls (WMD 1.53, 95% CI 1.02 to 2.32), with no significant heterogeneity between the studies ($\chi^2 = 3.21$, $p = 0.52$). Patients in the clopidogrel group had a small, significantly increased length of stay in hospital (WMD 1.18, 95% CI 0.24 to 2.12) but with significant heterogeneity between the studies ($\chi^2 = 31.87$, $p < 0.01$). Mortality did not differ significantly, but patients in the clopidogrel group had a significantly higher re-exploration rate and significantly increased ventilation requirement (table 1).

## DISCUSSION

The results of this meta-analysis of 11 (prospective and retrospective) studies suggest that postoperative complications, in terms of blood loss, transfusion requirements, adverse outcomes, length of hospital stay, re-exploration rate, and ventilatory requirements, increased significantly for patients taking clopidogrel undergoing cardiac surgery. Mortality, however, did not differ significantly due to the use of clopidogrel. No published meta-analyses have evaluated these data. The use of meta-analytical techniques allowed the inclusion of a large number of participants (4002

**Table 1** Results of meta-analysis

| Outcome | No in analysis | | WMD/OR (95% CI) | Heterogeneity values | | Overall effect | |
|---|---|---|---|---|---|---|---|
| | CL | NCL | | $\chi^2$ | $\chi^2$ p value | Z | Z p value |
| Blood loss | 427 | 2636 | 323.62 (137.19 to 510.04) | 325.94 | <0.01 | 3.40 | <0.01 |
| Overall transfusion risk | 767 | 2021 | 4.90 (2.79 to 8.59) | 64.73 | <0.01 | 5.54 | <0.01 |
| Overall transfusion requirement | 1542 | 1239 | 1.36 (0.80 to 1.92) | 1208.14 | <0.01 | 4.78 | <0.01 |
| Mortality | 333 | 1005 | 1.01 (0.41 to 2.48) | 1.76 | 0.78 | 0.02 | 0.98 |
| Adverse events | 296 | 874 | 1.53 (1.02 to 2.32) | 3.18 | 0.53 | 2.04 | 0.04 |
| Length of stay | 229 | 1994 | 1.18 (0.24 to 2.12) | 31.87 | <0.01 | 2.47 | 0.01 |
| Re-exploration rate | 445 | 2649 | 6.76 (3.37 to 13.56) | 2.63 | 0.85 | 5.38 | <0.01 |
| Ventilation requirement | 210 | 597 | 2.81 (1.63 to 4.86) | 3.97 | 0.14 | 3.70 | <0.01 |

CI, confidence interval; CL, clopidogrel group; NCL, non-clopidogrel group (control); OR, odds ratio; WMD, weighted mean difference; Z, value for test for overall effect.

patients). Studying a sample of the size presented in this report would take considerable time and cost and would necessitate a multicentre randomised controlled trial design.

Previous studies have suggested that clopidogrel should be withheld even before coronary angiography until immediately before the procedure.[11] Clopidogrel for unstable patients is often regarded as optimal treatment to reduce ischaemic events, yet the results from this meta-analysis suggest that its use increases morbidity in patients who undergo coronary surgery. This may pose difficult clinical decisions to achieve a balance between reducing the increased risk of ischaemic events before surgery and the increased risk of bleeding during and after cardiac surgery and associated postoperative complications.

The findings from the present study should be treated with caution because no randomised trials comparing patients taking versus not taking clopidogrel in a coronary artery bypass graft population were available for inclusion. A limitation of this analysis is that the studies analysed were not matched for the clopidogrel and control groups. This includes the comparative level of operative experience between surgeons and the different risk profiles of patients in each group, especially regarding the distribution of factors (independent predictors) responsible for perioperative complications, ventilation requirements, and prolonged length of stay. These are factors that can significantly alter the effect size (odds ratios) and the precision (confidence intervals) of the overall estimate of the outcomes of interest.

This meta-analysis suggests that, although evidence from randomised trials is not available, clopidogrel may indirectly compromise hospital resources after coronary surgery by significantly increasing blood loss, transfusion and ventilation requirements, length of inpatient stay, and re-exploration rate. This may pose difficulty for clinicians weighing up the advantages of reducing ischaemic complications with the use of clopidogrel and avoiding perioperative coronary surgery complications after blood loss.

**Authors' affiliations**
**S Purkayastha, P Tekkis, A Darzi,** Imperial College, Department of Surgical Oncology and Technology, London, UK
**T Athanasiou, V Malinovski, R Casula, B Glenville,** Department of Cardiothoracic Surgery, St Mary's Hospital, London, UK
**R Foale,** Department of Cardiology, St Mary's Hospital, London, UK

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This quantitative meta-analysis was performed following the recommendations of the quality of reporting of meta-analyses (QUOROM) statement.

Correspondence to: Mr Thanos Athanasiou, St Mary's Hospital, Praed Street, London W2 1NY, UK; tathan5253@aol.com

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